UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,319	10/18/2005	Mira Susa Spring	PA/4-32899A	2731

75074 7590 10/01/2008

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
400 TECHNOLOGY SQUARE
CAMBRIDGE, MA 02139

EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
10/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,319	SUSA SPRING ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *1-6,8,10 and 12-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0607*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-51 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group III in the reply filed on 5/29/08 is acknowledged.

Accordingly, claims 1-6, 8, 10, 12-51 are withdrawn from consideration for being directed to non-elected subject matter. Claims 7, 9 and 11 are currently under examination.

Claim Objections

Claims 7, 9 and 11 are objected to for containing non-elected subject matter. The claims recite "at least one gene or a member of a gene family of Table 1" whereas Applicants elected Hey1 for such gene. Amending the claims such that they are only directed to elected inventions is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention:

The claims are drawn to a method of monitoring the treatment of a patient with a condition characterized by abnormal bone tissue deposition, abnormal rate of formation of osteoblasts or osteoporosis, comprising administering a pharmaceutical composition to the patient, preparing a gene expression profile from a cell or tissue sample from the patient, and or assaying an activity of a protein encoded by Hey1, comparing the profile or activity to the activity of a MC3T3-E1 or MC3T3-1b cell population or an osteoblastic differentiated MC3T3-E1 or MC3T3-1b cell population.

The breadth of the claim:

The breadth of the claim is very broad. The instant claims are drawn to such method of comparing the expression of mRNA or protein level of Hey 1 from patient suffering from any type of disorder characterized by abnormal bone tissue deposition, abnormal rate of formation of osteoblasts and osteoporosis, and treated with any type of pharmaceutical agent, to the

expression of mRNA and protein in either differentiated or un-differentiated MC3T3-E1 or MC3T3-1b cells.

The teaching and guidance from the specification and the presence of working examples:

The specification discloses comparing the expression profile between non-differentiated MC3T3-1b cells and GP/AA/BMP-2 stimulated MC3T3-1b cells on day 1 and day 3 following stimulation by using microarray analysis. The specification discloses this clone is selected based on its fast and efficacious differentiation capability. The specification further lists genes which expression up or down regulates following stimulation, including Hey 1, which is up-regulated following stimulation. The specification also discloses that this gene, a member of the notch signaling pathway, is induced by BMP-2, and inhibition of Hey 1 affects long term mineralization. However, the specification fails to teach a nexus between the expression of Hey 1 and any of the disorder involves bone tissue deposition, abnormal rate of formation or osteoporosis. The specification fails to teach the relationship between monitoring the expression of Hey 1, either at mRNA or protein level, in a patient with such disorder, comparing to the level of Hey 1 in either differentiated or non-differentiated MC3T3-1E or MC3T3-1b cells, would help to indicate the effectiveness of the pharmaceutical agent. In other words, if there is a increase/decrease in the expression, what would it mean with regard to the treatment of the pharmaceutical agent. Moreover, the specification only established the increase of expression at mRNA level, but not the activity of the protein. As such, whether the claimed method may be practice without undue experimentation is unpredictable.

The state of prior art and the level of predictability in the art:

The state of prior art establishes that Hey1 is a BMP target protein. Korchynskyi et al. (Journal of Bone and Mineral Research, 2003, vol. 18, no.7, pages 1177-1185) teach that Hey1 is up-regulated following BMP stimulation in C2C12 myoblasts differentiation into osteoblast like cells (see abstract). Liu et al. (Journal of Cellular Physiology, 2007. Vol. 211, pages 728-735), a more recent publication, further teach that Hey1 mRNA is up-regulated in Runx2-deficient cell lines following BMP-2 stimulation, whereas the role of Hey1 during osteoblast differentiation requires further study (see page 734, col.2, 1st paragraph). However, a review of the state of art at the time of filing does not teach how Hey1 is related to any disease that involves abnormal tissue deposition, abnormal rate of formation of osteoblasts and osteoporosis. The art is also silent on how to monitoring the treatment of such disease by comparing the expression of Hey1 to that of a cell line, namely MC3T3-E1 or M3T3-1b.

Based on the teaching of the prior art, whether comparing the expression or activity of Hey1 from a patient suffering from a disease that involves abnormal tissue deposition, abnormal rate of formation of osteoblasts and osteoporosis with the expression of Hey1 in the MC3T3 cell line can monitor the treatment of said disease is unpredictable. According to the disclosure of the specification, the expression of Hey1 is induced at different level at day 1 and day 3 in 3T3 1b cells (8 and 3 fold), whereas the induction level is also different in different cell line such as RD-C6 cells (13.8 fold) (Liu et al., Table 2), it is unclear how the reference level of expression will be determined when using different clones of MC3T3 cells, and which time period of following induction will be used. In other words, the specification fails to teach how to establish a reference for such comparison so that the comparison would be meaningful for the monitoring of the therapy. For the lack of teaching from the specification and inadequate information from

the prior art, the nexus between Hey1 expression and diseases involving abnormal tissue deposition, abnormal rate of formation of osteoblasts and osteoporosis does not exist. As such, the skilled artisan would have to engage in undue experimentation to establish such a nexus, and practice the method as claimed. Therefore, the claimed invention is not enabled by the instant specification.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joe Woitach Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian Ph.D./

Primary Examiner, Art Unit 1636